REMARKS

The Present Invention and the Pending Claims

The present invention is directed to compounds comprising the Dmt-Tic pharmacophore, related compositions and methods of use. Claims 1-10 are pending.

The Amendments to the Claims

The claims have been amended to point out more particularly and claim more distinctly the present invention. In particular, claim 1 has been amended to recite that Y comprises a benzoimidazolyl group, as supported by the specification at, for example, paragraph [0031]. Claims 5, 7, 8 and 10 have been amended as supported by the specification at, for example, paragraphs [0042] through [0045]. No new matter has been added by way of these amendments.

The Office Action

Claims 5-8 and 10 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Claims 1 and 3 have been rejected under 35 U.S.C. § 102(b), as allegedly anticipated by U.S. Patent 5,773,881 (Schiller) ("the '881 patent") and U.S. Patent 5,602,099 (Schiller) ("the '099 patent"). In addition, claims 1 and 3 have been rejected under 35 U.S.C. § 103(a), as allegedly obvious in view of Guerrini et al. (*Bioorg. Med. Chem.*, 6: 57-62 (1998)). Claims 2, 4, and 9 have been allowed.

Discussion of the Enablement Rejection

Claims 5-8 and 10 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Specifically, the Office contends that the specification does not provide evidence that the compounds of claims 5-8 and 10 have a therapeutic effect, such as treating analgesia. However, the Office states that "[a]s for the 'state of the art', there are examples of compounds which are effective to antagonize the *delta*-opioid receptor *in vitro*, and which also induce analgesia" (Office Action, page 3, first full paragraph). In making such a statement, the Office acknowledges that the state of the art is such that one of ordinary skill in the art would reasonably believe that a compound that antagonizes the *delta*-opioid receptor *in vitro* also induces analgesia. In other words, compounds that antagonize the *delta*-opioid receptor *in vitro* have therapeutic efficacy *in vivo*. This, coupled with the teachings of the instant specification can only lead one to conclude that the instant specification is, in fact, enabling for a method of treating a mammal as claimed in claims 5-8 and 10.

The Office has not met the requirement for a proper *prima facie* case of lack of enablement. While the Office cites various literature references in an effort to contend that *in vitro* results do not always provide *in vivo* efficacy, and that, therefore, claims 5-8 and 10 are not enabled, applicants point out that several of the cited references relate to completely different methods (e.g., stimulation of growth hormones, cAMP production in cells, and inhibition of the MSH receptor relating to melanogenesis) and all of the references relate to compounds that are structurally different from those recited in claims 5-8 and 10. Moreover, it should be noted that the cited references do *not* indicate that *in vitro* potency is not indicative of *in vivo* efficacy. Instead, the references indicate that increased *in vitro* binding affinity did not always *correlate* with increased *in vivo* efficacy. This does not constitute a teaching that such compounds are necessarily without therapeutic effect. Rather, this merely suggests that the degree of effectiveness of such compounds may vary.

Even assuming that the Office meets its burden of establishing a proper *prima facie* showing of lack of enablement, applicants' disclosure is more than ample to rebut such a showing. In order for an invention to be considered enabled, applicants need only teach those of ordinary skill in the art how to make and use the present invention. In this regard, applicants point out that Example 75 of the instant specification describes the *in vitro* efficacy of the compounds of claims 5-8 and 10 in binding to the δ-opioid and/or μ-opioid receptor. A condition that can be treated by such antagonism is described in the specification at, for example, paragraph [0044]. Chemical synthesis of the compounds recited in claims 5-8 and 10 is described in the specification at, for example, the Example section, such as Examples 59, 65, 69, and 73. Suitable doses are described in the specification at, for example, paragraphs [0046] through [0051]. Formulations are described in the specification at, for example, paragraphs [0034] through [0041], and includes modes of administration, carriers, and excipients. The instant specification also teaches that conventional techniques, such as the tail flick test described at, for example, paragraph [0050], are routinely used to determine *in vivo* efficacy. Therefore, no undue experimentation would be required for one of ordinary skill in the art to practice the method of claims 5-8 and 10, and the state of the art provides a reasonable expectation of success.

Accordingly, applicants maintain that claims 5-8 and 10 are enabled by the specification for a method of treating a mammal in need thereof. However, in an effort to advance prosecution, claims 5-8 and 10 have been amended as indicated above. Applicants maintain the right to pursue method of treatment claims in subsequent applications. In view of the foregoing, the rejection should be withdrawn.

Discussion of the Anticipation Rejection

Claims 1 and 3 have been rejected under 35 U.S.C. 102(b), as allegedly anticipated by U.S. Patent 5,733,881 (Schiller) ("the '881 patent") and U.S. Patent 5,602,099 (Schiller) ("the '099 patent"). The '881 patent discloses the compound Dmt-Tic-Cha-Phe-OH, and the '099 patent discloses the compound Dmt-Tic-Phe-Phe-NH_2. Both compounds allegedly anticipate the compound of claim 1, since in the claimed compound X is a spacer group comprising at least one amino acid residue (e.g., Cha or Phe) and Y comprises an aromatic group (e.g., Phe).

Claim 1 has been amended such that Y comprises a benzoimidazolyl group. Neither the '881 patent, nor the '099 patent describe any compounds that contain a benzoimidazolyl group. In view of this amendment, it is submitted that the anticipation rejection has been overcome.

The '881 and '099 patents also do not render the compound of claim 1 obvious. These references only describe a phenyl aromatic compound and do not teach or suggest a heteroaryl compound of any type, let alone specifically teach a benzoimidazolyl group. Thus, claims 1 and 3 are novel and unobvious in view of these references.

Discussion of the Obviousness Rejection

Claims 1 and 3 have been rejected under 35 U.S.C. 103(a), as allegedly obvious in view of Guerrini et al. (*Bioorg. Med. Chem.*, 6: 57-62 (1998)). Guerrini et al. allegedly discloses the compound [Dmt^1, Tic^2]DYN(1-11)NH_2. Since the first five amino acids of Dynorphin A are Tyr-Gly-Gly-Phe-Leu, the Office contends it would have been obvious to replace the first two amino acids with Dmt and Tic, as Guerrini et al. suggests, and prepare a compound of the structure Dmt-Tic-Gly-Phe-Leu. The structure Dmt-Tic-Gly-Phe-Leu is reportedly encompassed by claims 1 and 3.

Claim 1 has been amended such that Y comprises a benzoimidazolyl group. Guerrini et al. does not describe any compounds that contain a benzoimidazolyl group. Since Guerrini et al does not teach or suggest every element of claims 1 and 3, it is submitted that the obviousness rejection in view of this reference has been overcome.

Information Disclosure Statement

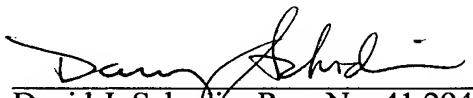
According to the Office Action, reference "BD" was stricken from the IDS because this reference may not have been obtained. In addition, the Office found a reference by Lazarus entitled "Size matters: New Frontiers in Designing potent delta-Opioid Antagonists,"

pages 24-29, but could not ascertain its origins. Applicants note that the reference found by the Office and authored by Lazarus is reference "BD," which consists of lecture notes from the International Symposium on Peptide Chemistry and Biology that took place in China in 1999. Accordingly, no journal title is associated with the Lazarus reference. Applicants request the Examiner to confirm consideration of this reference, listed as reference "BD" on the IDS submitted April 8, 2002 in the next Office Action.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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